

13-06-2001

X-12420

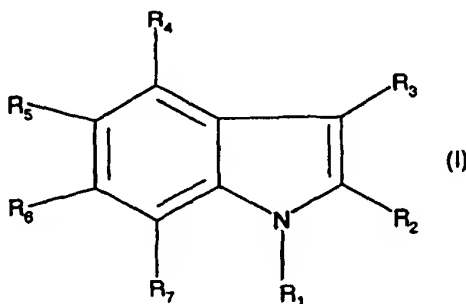
00944673.3(11-07-2000) US00/16319(11-07-2000)

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WE CLAIM:

1. An indole compound represented by the formula
(I), or a pharmaceutically acceptable salt, solvate, or
5 prodrug derivative thereof;



wherein ;

- 10 R_1 is selected from groups (a), (b), and (c)
wherein;

(a) is C7-C20 alkyl, C7-C20 haloalkyl, C7-C20
alkenyl, C7-C20 alkynyl, carbocyclic radical, or
heterocyclic radical, or

- 15 (b) is a member of (a) substituted with one or
more independently selected non-interfering
substituents; or

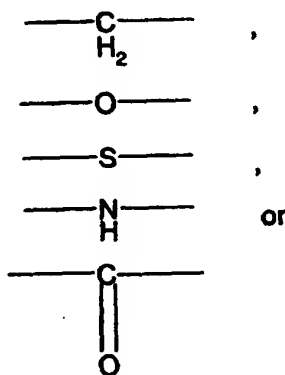
-111-

(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

5 R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

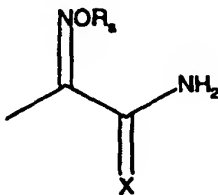
R_3 is $-(L_3)-Z$, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:

10

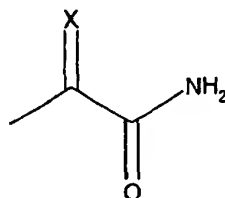


and Z is selected from a group represented by the formulae,

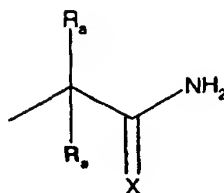
15



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or



5

wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈ alkoxy, aralkyl and -CN;

10 R₄ is the group, -(L_C)-(acylamino acid group); wherein -(L_C)-, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R₅ is selected from hydrogen, a non-interfering substituent, or the group, -(L_A)-(acidic group); wherein
15 -(L_A)-, is an acid linker having an acid linker length of 1 to 8;

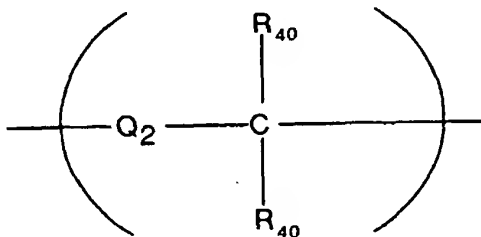
R₆ and R₇ are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s),

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heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

2. The compound of claim 1 wherein R₂ is
5 hydrogen, C₁-C₄ alkyl, C₂-C₄ alkenyl, -O-(C₁-C₃ alkyl),
-S-(C₁-C₃ alkyl), C₃-C₄ cycloalkyl, -CF₃, halo, -NO₂, -
CN, or -SO₃.

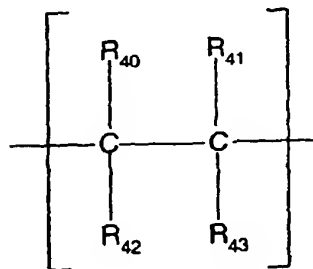
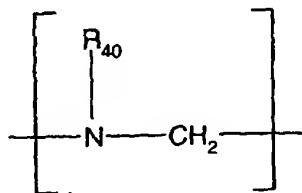
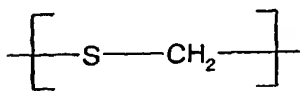
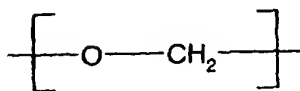
3. The compound of Claim 1 wherein the acylamino
10 acid linker group, -(L_C)-, for R₄ is selected from a
group represented by the formula;



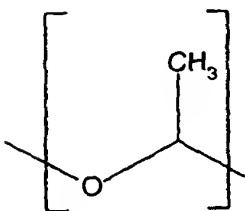
15 where Q₂ is selected from the group -(CH₂)-, -O-, -NH-,
-C(O)-, and -S-, and each R₄₀ is independently selected
from hydrogen, C₁-C₈ alkyl, aryl, C₁-C₈ alkaryl, C₁-C₈
alkoxy, aralkyl, and halo.

20 4. The compound of Claim 1 wherein the acylamino
acid linker group, -(L_C)-, for R₄ selected from -(L_C)-
is a divalent group selected from,

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or

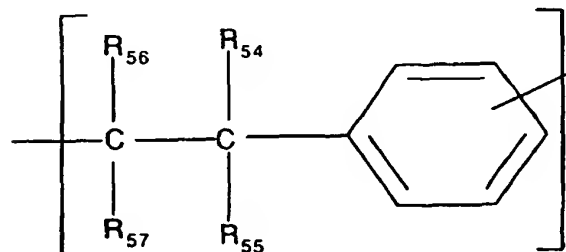
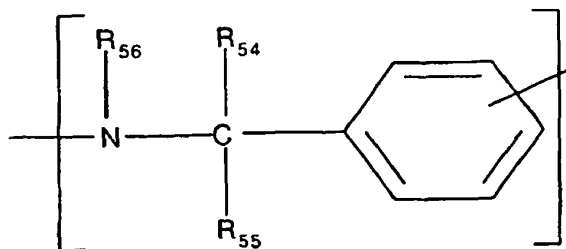
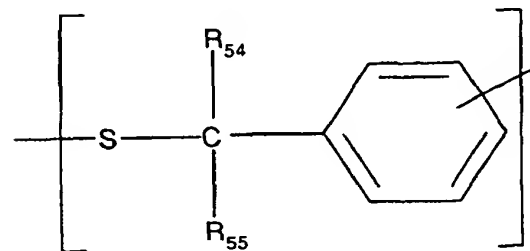
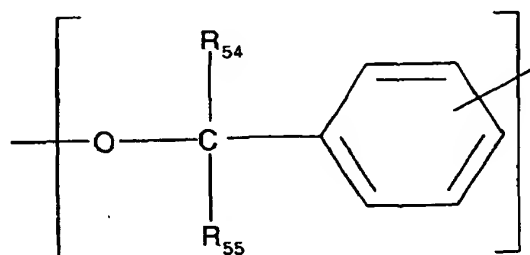


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where R₄₀, R₄₁, R₄₂, and R₄₃ are each independently selected from hydrogen, C₁-C₈ alkyl.

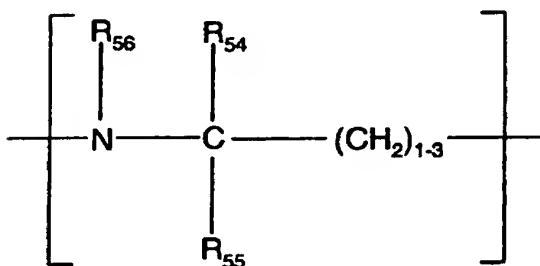
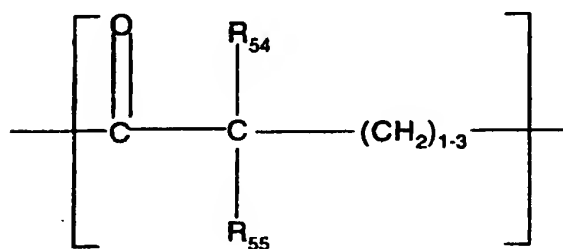
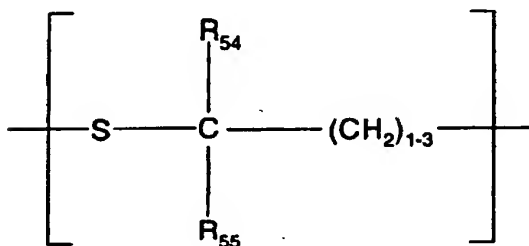
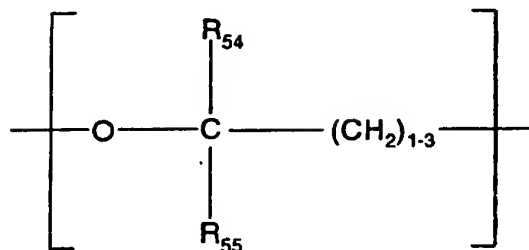
-115-

5. The compound of Claim 1 wherein the acid linker, $-(L_a)-$, for R_5 is selected from a group represented by the formulae consisting of;

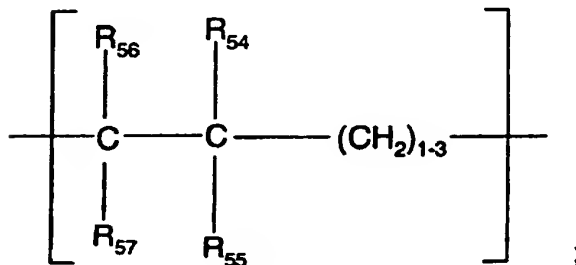


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and



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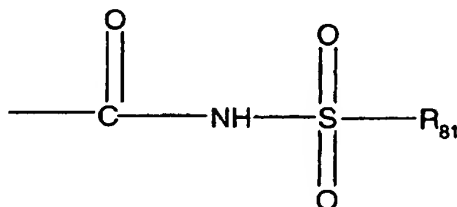
wherein R₅₄, R₅₅, R₅₆ and R₅₇ are each independently hydrogen, C₁-C₈ alkyl, C₁-C₈ haloalkyl, aryl, C₁-C₈ alkoxy, or halo.

- 5 6. The compound of claim 1 wherein R₅ is the group, -(L_a)-(acidic group) and wherein the (acidic group) is selected from the group:

-5-tetrazolyl,

10

-SO₃H,



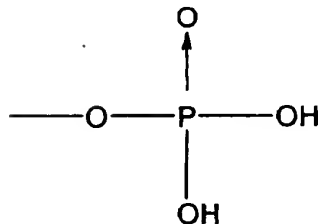
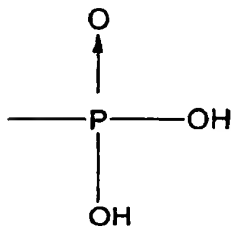
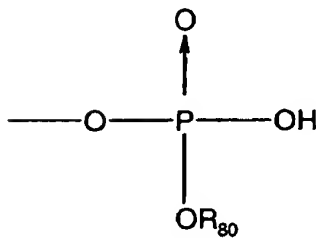
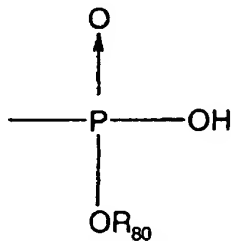
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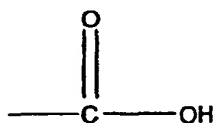
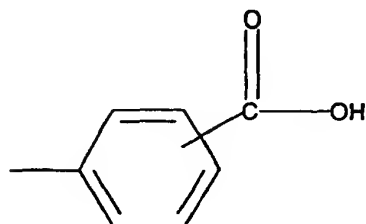


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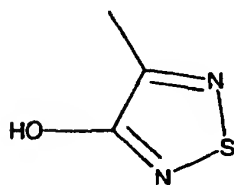
AMENDED SHEET

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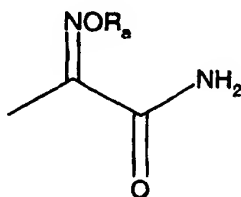


or



where R_{80} is a metal or C_1 - C_8 alkyl and R_{81} is an organic substituent or $-CF_3$.

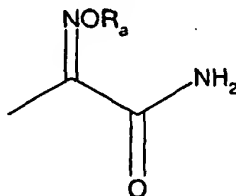
- 5 7. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



- and the linking group $-(L_3)-$ is a bond; and R_a is
10 hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl.

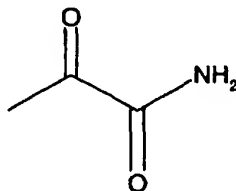
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8. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



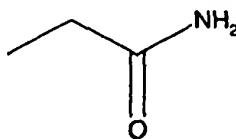
and the linking group $-(L_3)-$ is a bond; and R_a is hydrogen.

9. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



10 and the linking group $-(L_3)-$ is a bond.

10. The compound of claim 1 wherein for R_3 , Z is the group represented by the formula;



15 and the linking group $-(L_3)-$ is a bond.

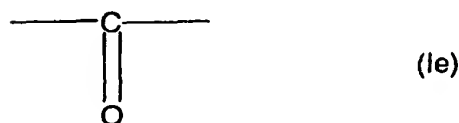
11. The compound of Claim 1 wherein, for R_6 the non-interfering substituent is hydrogen, C₁-C₈ alkyl,

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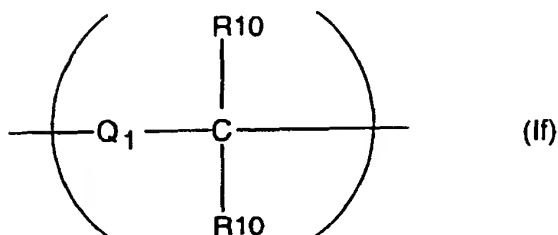
- C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₇-C₁₂ aralkyl, C₇-C₁₂ alkaryl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C₁-C₈ alkoxy, C₂-C₈ alkenyloxy, C₂-C₈ alkynyloxy, C₂-C₁₂ alkoxyalkyl, C₂-C₁₂ alkoxyalkyloxy, C₂-C₁₂ alkylcarbonyl, C₂-C₁₂ alkylcarbonylamino, C₂-C₁₂ alkoxyamino, C₂-C₁₂ alkoxyaminocarbonyl, C₁-C₁₂ alkylamino, C₁-C₆ alkylthio, C₂-C₁₂ alkylthiocarbonyl, C₁-C₈ alkylsulfinyl, C₁-C₈ alkylsulfonyl, C₂-C₈ haloalkoxy, C₁-C₈ haloalkylsulfonyl, C₂-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, -C(O)O(C₁-C₈ alkyl), -(CH₂)_n-O-(C₁-C₈ alkyl), benzyloxy, phenoxy, phenylthio, -(CONHSO₂R), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -(CH₂)_n-CO₂H, chloro, cyano, cyanoguanidiny, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO₃H, thioacetal, thiocarbonyl, or carbonyl; where n is from 1 to 8.

12. The compound of Claim 1 wherein for R₁ the divalent linking group -(L₁)- is selected from a group represented by the formulae (Ia), (Ib), (Ic), (Id), (Ie), and (If):

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or

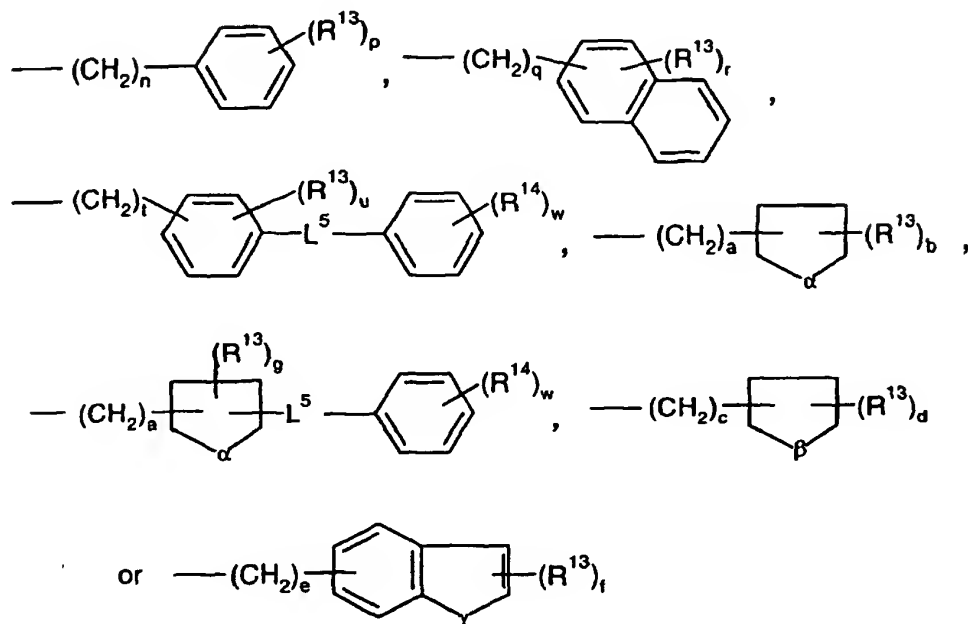


5 where Q_1 is a bond or any of the divalent groups Ia, Ib, Ic, Id, and Ie and R_{10} is independently -H, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

13. The compound of claim 1 wherein the linking
10 group $\text{---(L}_1\text{)---}$ of R_1 is $\text{---(CH}_2\text{)---}$ or $\text{---(CH}_2\text{---CH}_2\text{)---}$.

14. The compound of claim 1 wherein the linking
group $\text{---(L}_{11}\text{)---}$ of R_{11} is a bond and R_{11} is $\text{---(CH}_2\text{)}_m\text{---R}^{12}$
wherein m is an integer from 1 to 6, and R^{12} is a group
15 represented by the formula:

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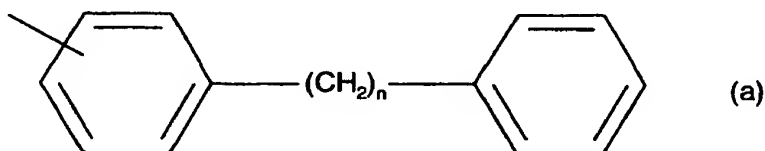


wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkoxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)_v-$, $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group

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consisting of C₁ to C₆ alkyl, C₁ to C₈ alkyloxy, C₁ to C₈ haloalkyloxy, C₁ to C₈ haloalkyl, aryl, and a halogen..

15. The compound of claim 1 wherein for R₁ the
5 group R₁₁ is a substituted or unsubstituted carbocyclic radical selected from the group consisting of cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenyl,
10 diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):

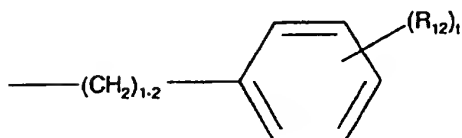


where n is a number from 1 to 8.

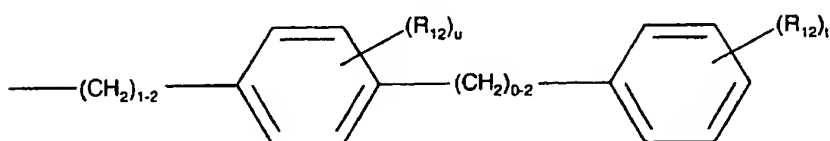
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16. The compound of Claim 12 wherein for R₁ the combined group $-(L_1)-R_{11}$ is selected from the groups;

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or



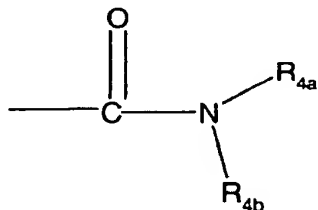
where R_{12} is a radical independently selected from halo, C_1 - C_{10} alkyl, C_1 - C_{10} alkoxy, $-S-(C_1-C_{10} \text{ alkyl})$, and C_1 -
 5 C_{10} haloalkyl, C_1 - C_{10} hydroxyalkyl and t is a number
 from 0 to 5 and u is a number from 0 to 4.

17. The compound of claim 1 wherein for R_1 the
 radical R_{11} is a substituted or unsubstituted
 10 heterocyclic radical selected from pyrrolyl,
 pyrrolodinyll, piperidinyll, furanyl, thiophenyl,
 pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl,
 isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, indolyl,
 carbazolyl, norharmanyl, azaindolyl, benzofuranyl,
 15 dibenzofuranyl, dibenzothiophenyl, indazolyl,
 imidazo(1,2-A)pyridinyl, benzotriazolyl, anthranilyl,
 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl,
 purinyl, pyridinyl, dipyridyl, phenylpyridinyl,
 benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl,
 20 pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl,

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quinazolinylmorpholino, thiomorpholino, homopiperazinyl,
tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-
dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl,
tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-
5 dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidiny,
hexamethyleneiminium, heptamethyleneiminium, piperazinyl
or quinoxaliny.

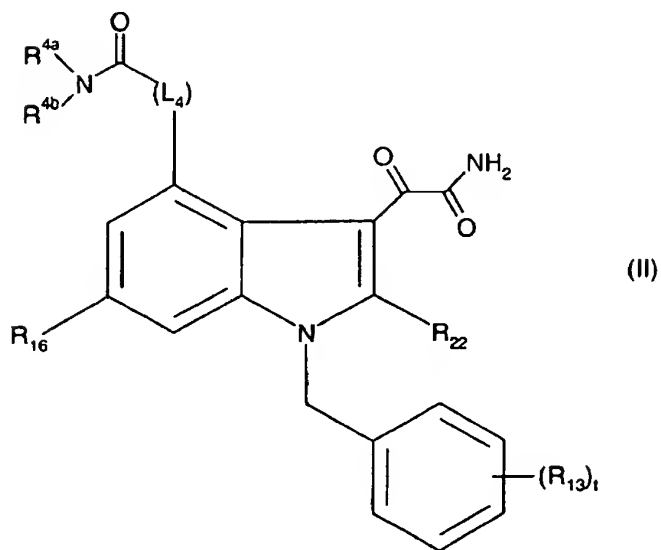
18. The compound of claim 1 wherein R₄ is the
10 group, -(L_C)-(acylamino acid group) and wherein the
(acylamino acid group) is:



15 and R^{4a} is selected from the group consisting of H, (C₁-
C₆)alkyl, (C₁-C₆)alkoxy, heteroaryl and aryl; and wherein
NR^{4b} is an amino acid residue with the nitrogen atom being
part of the amino group of the amino acid.

20 19. An indole compound represented by the
formula (II), or a pharmaceutically acceptable salt,
solvate, or prodrug derivative thereof;

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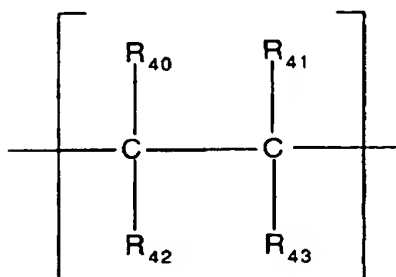
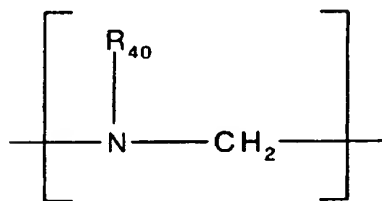
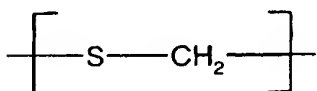
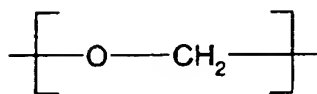
5 wherein ;

R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF₃, -Cl, -Br, or -O-CH₃;

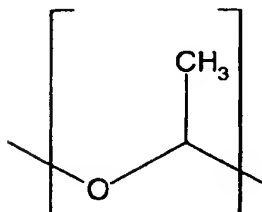
R^{4a} is hydrogen; and

10 NR^{4b} is an amino acid residue with the nitrogen atom being part of the amino group of the amino acid, and -
(L_C)- is a divalent group selected from;

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or



5 where R₄₀, R₄₁, R₄₂, and R₄₃ are each independently selected from hydrogen or C₁-C₈ alkyl.

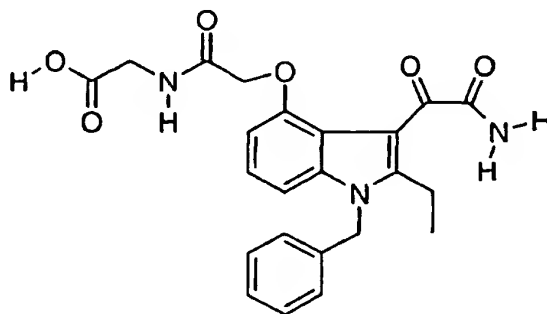
R₁₆ is selected from hydrogen, C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkylthio C₁-C₈ haloalkyl, C₁-C₈
10 hydroxyalkyl, and halo.

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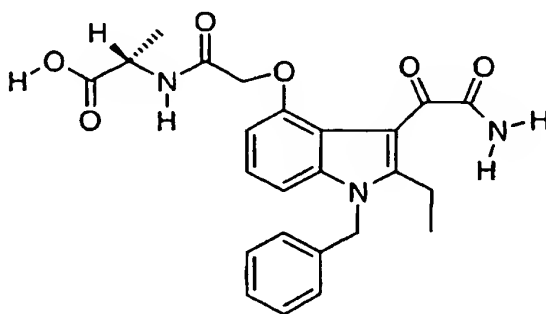
R_{13} is selected from hydrogen and C₁-C₈ alkyl, C₁-C₈ alkoxy, -S-(C₁-C₈ alkyl), C₁-C₈ haloalkyl, C₁-C₈ hydroxyalkyl, phenyl, halophenyl, and halo, and t is an integer from 0 to 5.

5

20. An indole compound represented by the formulae (C1), (C2), (C3), (C4), (C5), (C6), (C7), (C8), (C9), (C10) or (C11);



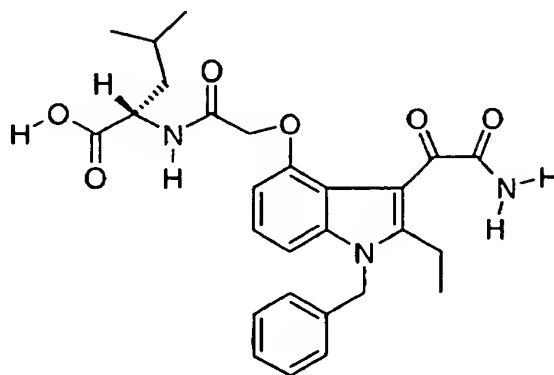
(C1),



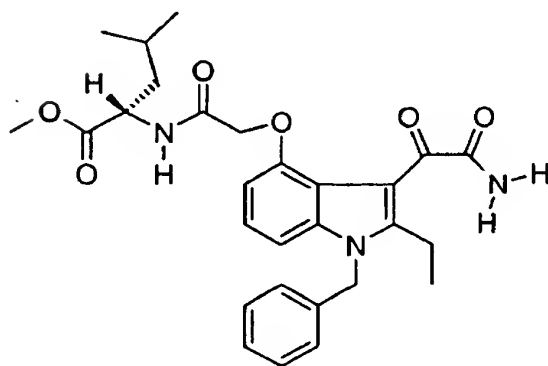
(C2),

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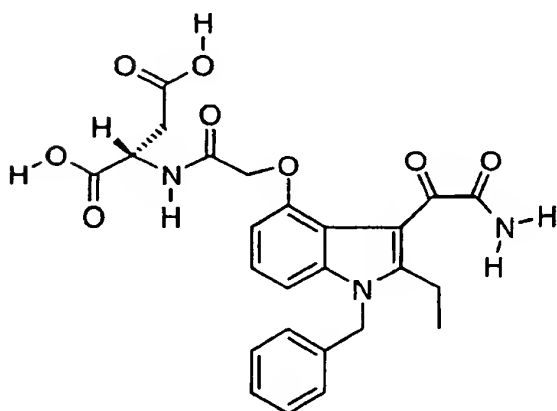
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(C3) ,



(C4) ,



(C5) ,

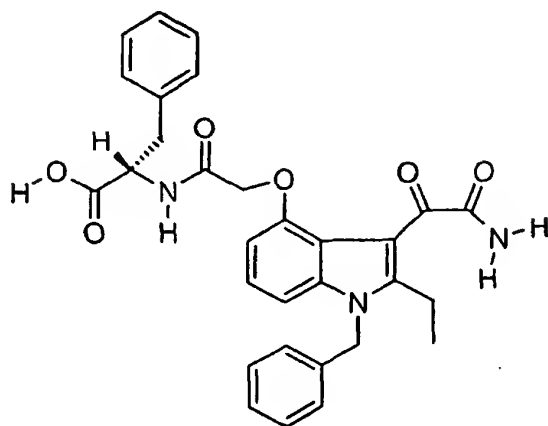
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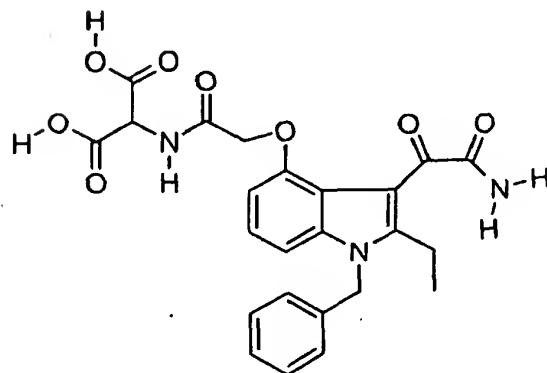
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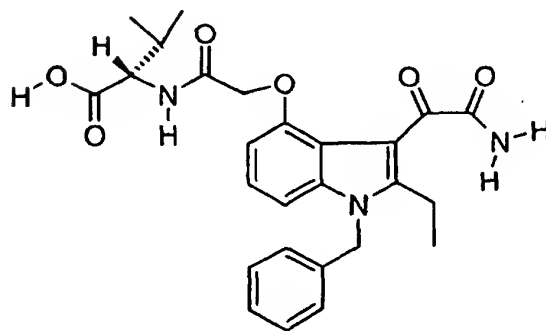
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(C6),



(C7),



(C8),

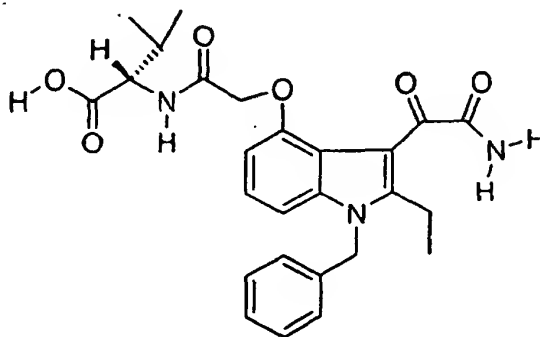
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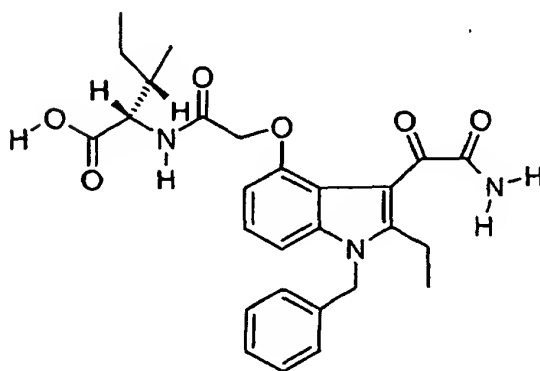
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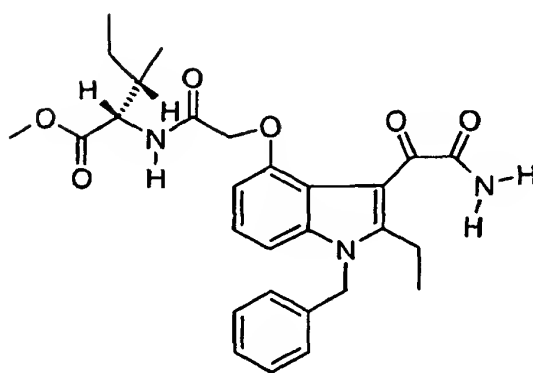
-132-



(C9),



(C10) and



(C11)

or pharmaceutically acceptable salts or prodrugs thereof.

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20. A compound of claim 1 selected from the group
consisting of:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]glycine ;

5 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]glycine;

10 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-alanine;

15 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

20 N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

10 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

15 [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

20 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

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N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

5 *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-
1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

2¹. A pharmaceutical formulation comprising a indole
compound as claimed in claim 1 together with a
10 pharmaceutically acceptable carrier or diluent therefor.

2². A method of inhibiting sPLA₂ mediated release
of fatty acid which comprises contacting sPLA₂ with a
therapeutically effective amount of indole compound as
15 claimed in claim 1.

2³. A method of treating a mammal, including a
human, to alleviate the pathological effects of
Inflammatory Diseases; wherein the method comprises
20 administration to said mammal of at least one indole
compound as claimed in Claim 1 in a pharmaceutically
effective amount.

2⁴. A compound of claim 1 or a pharmaceutical
25 formulation containing an effective amount of the

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compound of claim 1 in treatment of Inflammatory Diseases.

25. A compound of claim 1 or a pharmaceutical formulation containing an effective amount of the compound of claim 1 for use as an inhibitor for inhibiting sPLA₂ mediated release of fatty acid.

26. Use of a pharmaceutical composition comprising sPLA₂ inhibitor compounds according to Claim 1 and mixtures thereof for the manufacture of a medicament for the therapeutic treatment of Inflammatory Diseases.